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Review Article

Current evidence of oral anticoagulant reversal: A systematic review

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ABSTRACT

Introduction: Approximately 4–6% of patients treated with oral anticoagulants (OAC) will suffer from major hemorrhage or be in need of urgent surgery necessitating anticoagulant reversal therapy. Several new oral anticoagulants and reversal agents have been introduced that make it difficult for physicians to stay updated on the current evidence of reversal management. This study aims to review the recent literature on oral anticoagulation reversal therapy and to present the current evidence in an easily approachable manner.

Materials and methods: A systematic literature search was conducted using PubMed and EMBASE to identify the latest publications on both vitamin K antagonist (VKA) and direct oral anticoagulant (DOAC) reversal strategies. All studies on humans who received any acute reversal management of VKA treatment were included, except case studies. Since only two studies on acute reversal of DOAC treatment have been published, clinical trials on healthy volunteers were also included.

Results: Twenty-one studies with a total of 4783 VKA treated patients, and 12 studies with a total of 529 DOAC treated patients were included. Elevated INR values due to VKA treatment could be reversed (INR ≤ 1.5) in 63.1% (95% CI: 61.0–65.2) of study subjects after treatment with 4F-PCC, as compared with 12.2% (95% CI: 8.2–16.2) after treatment with fresh frozen plasma (FFP), ($p < 0.001$). Thromboembolism occurred in 1.6% (95% CI: 1.2–2.1) of VKA-patients treated with 4F-PCC, and in 4.5% (95% CI: 2.3–6.7) of FFP-treated patients. To date, reversal of laboratory parameters has been demonstrated for two reversal agents specific to DOACs: idarucizumab for dabigatran reversal and andexanet-alfa for factor Xa-inhibitor reversal.

Conclusions: This review supports the use of PCC for VKA reversal, specifically for 4F-PCC over FFP for laboratory reversal. There are no studies on clinical efficacy of non-specific agents for DOAC reversal and the evidence for laboratory reversal is not consistent.

1. Introduction

Millions of patients worldwide are treated with oral anticoagulation therapy (OAC), primarily for prevention of stroke in patients with atrial fibrillation (AF). Vitamin K antagonists (VKA), e.g. warfarin, is by far the most commonly used OAC agent and has long constituted the only alternative for OAC treatment [1]. However, in 2010 the activated thrombin (FIIa) inhibitor dabigatran was approved by the Food and Drug Administration, FDA, as an alternative to VKA, and since then an additional three non-vitamin K oral anticoagulants (DOACs) have been approved for use. These are all activated factor X (FXa)-inhibitors-apixaban, rivaroxaban, and edoxaban. Since their introduction on the market, the DOACs have steadily increased in popularity, For example in the United Stated, their use matched that of warfarin in 2014 [2]. Unlike VKA, the DOACs have a wide therapeutic range, predictable response effect and few food and drug interactions. The DOACs also have a more rapid onset (1–4 h) and a shorter half-life (7–12 h) than VKA. However, reversal of DOAC effect is naturally not nearly as well studied as with VKA. Around 2–4% of all OAC treated patients will suffer a major hemorrhage, and an additional 2% will need urgent invasive procedure that could require reversal of the anticoagulative effect [3]. Hence, there is a need for evidence-based reversal strategies, as well as precise tools to measure the effect of anticoagulants. Clinical outcomes in acute bleeding may be the most relevant measures of safety and efficacy of anticoagulant reversal strategies, but patients in need of acute reversal therapy are rare and with diverse disease profiles, which

Abbreviations: OAC, Oral anticoagulant; VKA, Vitamin K antagonist; DOAC, Direct oral anticoagulant; PCC, Prothrombin complex concentrate; 4F-PCC, Four factor PCC; 3F-PCC, Three factor PCC; aPCC, Activated PCC; FFP, Fresh frozen plasma; AF, Atrial fibrillation; TE, Thromboembolism; VTE, Venous thromboembolism; FIIa, Activated factor II; FXa, Activated factor X; rFVIIa, Recombinant activated factor VII; TTR, Time in therapeutic range; PT, Prothrombin time; INR, International Normalized Ratio; aPTT, Activated partial thromboplastin time; ECT, Ecarin clotting time; ETP, Endogenous thrombin potential; dTT, Diluted thrombin time; ICH, Intracranial hemorrhage; SBU, Statens beredning för medicinsk och social utvärdering (Swedish Agency for Health Technology Assessment and Assessment of Social Services); SEK, Swedish kronor

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make clinical outcome difficult to standardize. Furthermore, a reduction of the bleeding (and thus the efficacy of the treatment) does not necessarily correlate with a beneficial clinical outcome. For these reasons, surrogate measurements in the form of laboratory values are often used to evaluate the result of a given treatment. International Normalized ratio (INR) is an established and standardized test that reflects the degree of the anticoagulative effect of VKA treatment. No equivalent is yet present for DOACs. Due to the many recent, and undergoing, developments of OAC and its reversal treatments, cause for uncertainty is likely to exist among the treating physicians, and the costs of these reversal agents demand a thorough evaluation of the advantage and effect to match its purpose and cost. This study aims to review the latest publications on oral anticoagulation reversal therapy, and to present the current evidence in an easily understandable manner, which hopefully will be of use to both the individual physician as well as the guideline decision makers.

2. Material and methods

2.1. Study identification

The report was prepared based on the PRISMA statement [4]. A systematic literature search was conducted in the PubMed and EMBASE electronical databases. The goal was to identify all published articles that presented outcome measures from real life patients treated with urgent reversal therapy reversal of oral anticoagulative treatment. Two separate searches were performed, one search targeting studies related to VKA-reversal, and one search targeting studies related to DOAC-reversal. For DOAC reversal treatment, only two published studies were identified. Therefore, the DOAC-search was expanded to also include clinical trials on healthy volunteers. The VKA search ranged from December 31st, 2005 to October 31st, 2016. The DOAC search ranged from December 31st, 2010 to October 31st, 2016. The searches were restricted to publications in the English language. The complete search strategy is presented in Supplementary Table 1. The search strategy was complemented by a manual search, where potentially interesting articles from reference lists of relevant publications were included.

2.2. Study selection

The aim of the search strategy was to identify studies including real life patients treated with acute reversal therapy. The following criteria were to be met for eligibility of a publication: availability of type (and preferably dose) of OAC therapy, availability of type (and preferably dose) of reversal agent and clinical and/or laboratory outcome measures used. Only human studies were considered, and for studies with multiple publications, only the latest publication was included. Case reports of individual patients were excluded.

2.3. Assessment of study validity

The randomized clinical trials (RCTs) were assessed with a quality assessment tool produced by the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU), which conforms to the recommendations in the PRISMA statement [4]. There is controversy regarding quality assessment of observational studies, especially studies without a control group, since these generally are regarded as being of low quality [5]. However, as the great majority of identified studies were of observational design, an assessment tool for the observational studies was constructed to systematically identify potential confounders and risks of bias (Supplementary Table 2). The tool was modified from the observational study assessment template of SBU [6], and the quality assessment tool for observational studies developed by the American national institute of health [7] All studies were classified as either at “High”, “Moderate” or “Low” risk of bias. The results are presented in Supplementary Table 3.

2.4. Data extraction

Information on study type, year of publication, study subjects (n and clinical context), OAC treatment, reversal agent and dose, time of follow up, laboratory and clinical outcomes, Thromboembolic events and rates of deaths was extracted. Reported partial or fully non-governmental funding of the studies and authors with ties to pharmaceutical companies were compiled in Supplementary Table 3.

2.5. Statistics

Rates of thromboembolic events, deaths and successfully reversed INR values from the VKA-studies were combined to mean values. Rates were classified based on type of reversal agent. Fisher's test was used to compare outcomes for the difference between FFP and PCCs rates of successfully reversed INR values, where sufficient data was considered available. Considering the DOAC studies, sufficient studies to make any comparisons of results were not found. Heterogeneity across cohorts was evaluated by calculation of Cochrane's Q and the I^2 statistic [8]. Calculations were performed with the Comprehensive Meta-Analysis software. Confidence intervals estimation for mean values and Fisher's tests were performed with software provided by McCallum Layton [9].

3. Results

3.1. Search results

The two searches on PubMed and EMBASE generated a total of 2044 citations. After screening the titles 1967 citations were excluded. The remaining 77 publications where read and screened, and finally 26 studies remained that were considered eligible. Reasons for exclusion were lack of original data ($n = 11$), inclusion criteria not met ($n = 23$), case reports ($n = 1$) and ongoing studies without results ($n = 13$). Another 7 publications were added after a manual search. In total 12 studies from the DOAC literature search and 21 studies from the VKA literature search were included in the review. Of the DOAC publications, 10 studies were randomized controlled studies on healthy volunteers, and 2 were interim analyses of ongoing trials in real clinical settings on patients with acute need of reversal therapy as described above. All of the VKA publications studied reversal in patients in real clinical situations. Seventeen of the VKA publications are observational (6 retrospective and 11 prospective), and 4 are randomized trials. A flow chart of the identification, selection and exclusion is shown in Fig. 1 and Fig. 2. Characteristics of the included studies are summarized in Table 1 and Table 2.

3.2. Risk of bias assessment

Of the twenty-one VKA studies, 4 were considered to have a high risk of bias, one was considered to have a low risk of bias and 16 were considered to have an average risk of bias. Six of the studies reported no conflict of interest, and 13 reported that at least one of the authors had ties to pharmaceutical companies. Nine of the studies were partly or completely funded by companies manufacturing PCC-products. Seven of the 12 DOAC studies were considered to have a low risk of bias, the remaining five were considered to have an average risk of bias. Only one study reported no conflict of interest, and all except one were partly or completely funded by companies producing DOAC, DOAC antidotes or PCC. A table of risk of bias and conflict of interests is presented in Supplementary Table 3.

3.3. Study subjects

A total of 4783 patients were included in the VKA review and 529 patients in the DOAC review. In the DOAC studies 136 patients were from clinical settings receiving reversal treatment for intracranial